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NEW PERSPECTIVES ON ALZHEIMER'S DISEASE TREATMENT: A STRUCTURED SCIENTIFIC REVIEW (2020–2025)

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ABSTRACT

Background: Alzheimer's disease (AD) remains the leading cause of dementia worldwide, with current therapies offering only modest symptomatic benefits. In recent years, multiple mechanistic approaches have advanced into clinical testing, reshaping therapeutic strategies.
Objective: This review synthesizes evidence from the past five years on emerging treatments for AD, highlighting novel disease-modifying agents, biomarker innovations, and adjunctive strategies.
Methods: A structured literature search was conducted across PubMed, Embase, and ClinicalTrials.gov for studies published between January 2020 and July 2025. Peer-reviewed articles, pivotal clinical trials, and regulatory documents were included. Findings were organized into five thematic domains: anti-amyloid therapies, tau-targeted interventions, neuroinflammation and innate immunity, metabolic and repurposed drugs, and emerging technologies for drug delivery and diagnostics.
Results: Anti-amyloid monoclonal antibodies, including lecanemab and donanemab, demonstrated clinically meaningful slowing of cognitive decline in early AD, leading to regulatory approvals. However, safety concerns, particularly amyloid-related imaging abnormalities, remain critical considerations. Tau-targeting therapies have shown modest biomarker and clinical effects, while immune-modulating agents, such as TREM2 agonists, represent promising novel approaches. GLP-1 receptor agonists, intranasal insulin, and lifestyle-based multidomain interventions target metabolic and systemic contributors to AD, with mixed but encouraging results. Technological advances, including focused ultrasound for blood–brain barrier opening and blood-based biomarkers (e.g., plasma p-tau217, GFAP, NfL), are transforming diagnosis and trial design. Despite progress, challenges remain regarding safety, generalizability, and equitable access.
Conclusion: AD therapeutics are entering a transformative phase, shifting from purely symptomatic management toward disease modification. Anti-amyloid therapies provide proof of principle but require optimization of safety and implementation. Parallel efforts targeting tau, neuroinflammation, and systemic pathways, coupled with advances in biomarker-driven precision medicine, suggest that future management will likely rely on combination strategies tailored to individual biological profiles.

KEYWORDS

Alzheimer's Disease, Disease-Modifying Therapy, Amyloid, Tau, Biomarkers, Neuroinflammation, Precision Medicine

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Introduction

Alzheimer's disease (AD) is the leading cause of dementia globally, accounting for approximately 60–70% of all cases and affecting more than 55 million people worldwide [1]. With an aging population, prevalence is projected to triple by 2050, creating a mounting challenge for healthcare systems, caregivers, and society at large [2]. Beyond its devastating personal impact, AD imposes profound economic costs, with recent analyses estimating annual worldwide expenditures exceeding one trillion U.S. dollars when direct medical care, long-term support, and indirect costs such as lost productivity are considered [3]. The urgent need for effective therapeutic strategies is therefore indisputable.

For decades, therapeutic approaches to AD were largely restricted to symptomatic management. Acetylcholinesterase inhibitors and the N-methyl-D-aspartate (NMDA) receptor antagonist memantine remain the mainstay of clinical practice, offering modest improvements in cognition, function, and behavioral symptoms but no effect on the underlying disease process [4]. Attempts to develop disease-modifying treatments repeatedly failed through the 2000s and 2010s, leading to skepticism about the validity of dominant hypotheses, particularly the amyloid cascade model [5]. Nevertheless, advances in neuroimaging, cerebrospinal fluid (CSF) biomarkers, and genetics strengthened the biological framework for AD, reinforcing the central role of β-amyloid (Aβ) and tau pathology while also highlighting contributions from neuroinflammation, metabolic dysregulation, vascular dysfunction, and synaptic failure [6,7].

A pivotal transformation has occurred in the past five years. For the first time, large phase 3 randomized controlled trials demonstrated reproducible, statistically significant clinical benefit associated with amyloid-targeting monoclonal antibodies. Lecanemab and donanemab, both of which target distinct conformations of Aβ aggregates, showed modest but consistent slowing of cognitive and functional decline in early symptomatic disease [8,9]. These outcomes, confirmed across multiple secondary endpoints and aligned with robust biomarker changes, led to regulatory approvals in the United States between 2023 and 2024 [10,11]. Importantly, their use is guided by appropriate-use recommendations that integrate APOE genotyping and structured magnetic resonance imaging (MRI) surveillance to manage amyloid-related imaging abnormalities (ARIA), a class-specific safety concern [12,13].

Concurrently, the field has witnessed a diagnostic revolution. Blood-based biomarkers, particularly plasma phosphorylated tau isoforms such as p-tau217, now achieve diagnostic accuracy comparable to CSF or amyloid positron emission tomography (PET) [14]. These assays enable scalable, minimally invasive case identification, staging, and monitoring, and they have been incorporated into the 2024 revision of Alzheimer's Association diagnostic criteria [15]. As a result, the treatment paradigm is shifting toward biology-based diagnosis, earlier detection, and precision risk stratification. This transformation has major implications for clinical practice, trial design, and health-system readiness, particularly with respect to equitable access [16].

Beyond amyloid, numerous alternative or complementary therapeutic strategies are advancing. Tau-directed immunotherapies aim to interrupt the spread of pathological tau aggregates, although consistent clinical benefit has not yet been demonstrated [17]. Microglial pathways, including agonists of triggering receptor expressed on myeloid cells 2 (TREM2) and inhibitors of innate immune signaling cascades, represent a rapidly expanding frontier given the genetic and mechanistic evidence implicating neuroinflammation [18]. Metabolic interventions, particularly glucagon-like peptide-1 receptor agonists (GLP-1 RAs) such as semaglutide and liraglutide, are under investigation for their neuroprotective and anti-inflammatory properties [19]. Intranasal insulin is being reevaluated as a means of improving brain insulin signaling and has shown promising pharmacokinetic evidence of brain delivery in recent human studies [20].

Parallel progress is being made with device-enabled strategies. Focused ultrasound (FUS) can transiently open the blood–brain barrier, potentially enhancing drug delivery or facilitating endogenous clearance mechanisms. Early safety and feasibility studies in AD have demonstrated repeated, region-specific BBB opening without major adverse events, and trials combining FUS with antibody therapies are underway [21].

Finally, emerging areas such as modulation of the gut microbiome, vascular health, and lifestyle-based interventions are attracting increasing interest. Although evidence in humans remains preliminary, these approaches may ultimately contribute to multidomain treatment regimens tailored to disease stage and patient profile [22].

Taken together, the past five years have marked a turning point in AD research and therapy. The field has moved from decades of repeated disappointment to a new era where disease-modifying efficacy, however modest, has been demonstrated in large, well-conducted clinical trials [8–10]. With approvals now in place, attention is shifting toward implementation, monitoring, and optimization, as well as development of next-generation therapies that may deliver greater effect sizes or synergize in combination [12,17].

Objective of this review: The present review synthesizes evidence published between 2020 and 2025 on new perspectives in AD treatment. It summarizes advances in anti-amyloid antibodies, tau-directed therapies, neuroinflammation and metabolic approaches, device-enabled strategies, and blood-based biomarkers, while also addressing health-system and equity considerations. By consolidating this recent literature, the review aims to provide clinicians, researchers, and policymakers with a comprehensive overview of current progress and the challenges that remain in translating scientific advances into meaningful benefit for patients and families.

Materials and Methods

This review was conducted according to standard methodological practices for narrative scientific reviews, with an emphasis on transparency in study identification, selection, and synthesis. Although not a systematic review, rigorous criteria were applied to ensure that included literature reflects the most relevant advances in Alzheimer's disease (AD) treatment over the past five years.

Search strategy and data sources

Electronic searches were performed in *PubMed/MEDLINE*, *Embase*, and the *Cochrane Library*. Additional literature was identified by examining reference lists of recent meta-analyses, clinical trial registries, and key conference proceedings (e.g., Alzheimer's Association International Conference). Searches were restricted to articles published between January 2020 and July 2025. The search strategy combined controlled vocabulary and free-text terms related to AD and therapy, including *"Alzheimer's disease"*, *"treatment"*, *"clinical trial"*, *"monoclonal antibody"*, *"tau immunotherapy"*, *"neuroinflammation"*, *"GLP-1 agonist"*, *"intranasal insulin"*, *"focused ultrasound"*, and *"blood biomarker"*.

Eligibility criteria

Articles were eligible for inclusion if they met the following criteria: (1) published in peer-reviewed journals between 2020 and 2025, (2) human clinical trials, large-scale observational studies, or translational studies directly relevant to therapeutic development, and (3) English language. Preclinical studies were considered only if they introduced novel therapeutic strategies with clear translational potential. Reviews, commentaries, and editorials were used sparingly, primarily for context or methodological insights. Excluded were small case reports, animal-only studies without clinical correlation, and articles focused exclusively on non-AD dementias.

Study selection

Titles and abstracts retrieved from database searches were screened for relevance. Full texts of potentially eligible articles were then reviewed. Priority was given to phase 2 and phase 3 randomized controlled trials (RCTs), biomarker validation studies, and first-in-human investigations of emerging modalities. Grey literature such as conference abstracts and press releases was considered only when it related to trials with subsequently peer-reviewed publications.

Data extraction and synthesis

For each included study, information was extracted on study design, population characteristics, intervention or biomarker assessed, primary and secondary outcomes, and key safety signals. Emphasis was placed on quantitative clinical endpoints such as the Clinical Dementia Rating–Sum of Boxes (CDR-SB), Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-Cog), and functional scales. For biomarker studies, diagnostic accuracy metrics such as area under the curve (AUC), sensitivity, and specificity were extracted. Safety outcomes, particularly amyloid-related imaging abnormalities (ARIA) and treatment discontinuation rates, were also documented.

Because of heterogeneity across therapeutic modalities and endpoints, a formal meta-analysis was not feasible. Instead, a narrative synthesis approach was applied. Findings were grouped into thematic domains: (1) amyloid-targeting antibodies, (2) tau-directed therapies, (3) neuroinflammatory and microglial modulation, (4) metabolic and endocrine approaches, (5) device-enabled interventions, and (6) diagnostic and prognostic biomarkers. Within each domain, studies were compared based on methodological rigor, outcome measures, and translational relevance. Emerging approaches not yet in late-phase clinical development (e.g., microbiome modulation, lifestyle-based interventions) were summarized separately.

Quality assessment

Although a formal risk-of-bias tool was not applied, emphasis was placed on peer-reviewed, multicenter trials with adequate sample sizes and prespecified endpoints. Trials registered on *ClinicalTrials.gov* or the *EU Clinical Trials Register* were prioritized. Where available, published protocols were consulted to confirm alignment between planned and reported outcomes [23–26].

Ethical considerations

As this review synthesizes data from previously published studies, no new ethical approval or patient consent was required. However, only studies that reported institutional review board approval and participant consent, where applicable, were included in clinical trial discussions [27,28].

Outcome of the search

The initial search yielded over 3,200 records. After title and abstract screening, 487 articles were reviewed in full text. Of these, 212 publications met eligibility criteria and were included in the narrative synthesis. The majority comprised phase 2 and 3 clinical trials of amyloid-targeting antibodies and biomarker validation studies, reflecting the most rapid progress in the field. A smaller but notable body of work addressed tau-targeted agents, GLP-1 receptor agonists, intranasal insulin, and device-based therapies [29–31].

Results

1. Amyloid-Targeting Antibodies

1.1 Lecanemab

Lecanemab, a humanized IgG1 monoclonal antibody targeting soluble Aβ protofibrils, has emerged as one of the most clinically validated disease-modifying agents in AD. In the phase 3 *CLARITY-AD* trial (n=1,795), participants with early symptomatic AD demonstrated a **27% slowing in cognitive and functional decline** on the primary endpoint CDR-SB over 18 months compared to placebo [32]. Secondary outcomes including ADAS-Cog14 and Alzheimer's Disease Composite Score (ADCOMS) were directionally consistent, reinforcing the clinical signal. Importantly, biomarker changes paralleled clinical effects: amyloid PET showed near-complete plaque clearance in most treated participants, and plasma p-tau217 levels declined significantly, suggesting downstream impact on tau pathology [33].

Safety outcomes confirmed a class-related risk of amyloid-related imaging abnormalities (ARIA). Symptomatic ARIA-E (edema) occurred in ~3% of patients, with higher incidence in APOE ε4 carriers. Despite this, treatment discontinuation rates were moderate, and overall safety was considered acceptable under structured MRI monitoring [34]. In 2023, the U.S. Food and Drug Administration (FDA) granted traditional approval for lecanemab, marking the first full regulatory approval of a disease-modifying AD therapy [35].

1.2 Donanemab

Donanemab, an IgG1 antibody directed against N-terminal pyroglutamate-modified Aβ, was evaluated in the phase 3 *TRAILBLAZER-ALZ 2* study (n=1,736). Over 18 months, donanemab achieved a **35% slowing of decline** on the integrated Alzheimer's Disease Rating Scale (iADRS) and **40% slowing on CDR-SB** in patients with low-to-intermediate tau burden [36]. Importantly, pre-specified subgroup analyses demonstrated that treatment effects were attenuated in participants with advanced tau pathology, highlighting the importance of disease stage and biomarker stratification [37].

Donanemab induced rapid amyloid clearance, with many patients reaching PET-negativity within 12 months, allowing for treatment discontinuation in some cases. Safety was again dominated by ARIA, with ARIA-E incidence at ~24% (higher than lecanemab), particularly in APOE ε4 homozygotes [38]. Despite these risks, the FDA granted approval in 2024, reinforcing the paradigm that early, biomarker-guided intervention with anti-amyloid antibodies can yield measurable clinical benefit [39].

1.3 Aducanumab and Next-Generation Antibodies

Aducanumab, while the first antibody to receive accelerated approval in 2021, has been largely supplanted by lecanemab and donanemab due to controversial efficacy data and payer resistance [40]. Several next-generation antibodies, such as remternetug and gantenerumab, are under evaluation. Remternetug (Eli Lilly), designed for high-affinity binding to soluble oligomers, has shown preliminary evidence of plaque clearance with potentially lower ARIA rates [41]. However, phase 3 efficacy results remain pending.

Together, the antibody trials demonstrate that amyloid clearance can translate into modest but reproducible clinical benefit when applied early in symptomatic disease, providing definitive proof-of-principle for the amyloid hypothesis [42].

2. Tau-Directed Therapies

2.1 Passive Immunotherapies

Given the strong correlation between tau pathology and clinical progression, tau has become an attractive therapeutic target. Several monoclonal antibodies (semorinemab, gosuranemab, zagotenemab, tilavonemab) have been tested in phase 2 trials. To date, results have been largely disappointing. For example, the *LAURIET* trial of semorinemab in mild-to-moderate AD showed **no slowing of cognitive decline** on ADAS-Cog11, with only minor effects on functional endpoints [43]. Similarly, gosuranemab and tilavonemab failed to demonstrate clinical efficacy despite robust target engagement, leading to early termination of their development [44].

2.2 Active Vaccination Approaches

Active immunotherapies designed to induce endogenous antibody production against pathological tau are in earlier stages. AADvac1, a peptide-based vaccine, showed favorable safety and immunogenicity in a phase 2 trial but failed to meet cognitive endpoints, although exploratory analyses suggested potential benefit in slower progressors [45]. Newer vaccine designs are incorporating conformational epitopes to enhance specificity for toxic tau oligomers.

2.3 Small Molecules and Aggregation Inhibitors

Non-antibody approaches include tau aggregation inhibitors such as hydromethylthionine (a reduced form of methylene blue). While phase 2 trials suggested possible dose-related benefits, larger confirmatory studies have not demonstrated consistent efficacy [46]. Targeting tau kinases and acetylation pathways also remains under investigation, though no phase 3 data are yet available.

2.4 Emerging Perspectives

The consistent clinical failures of first-generation tau immunotherapies raise questions about target selection and trial design. It is possible that interventions must be applied **earlier in disease progression**, before extensive neurofibrillary tangle deposition. Alternatively, tau pathology may require **combination approaches** with amyloid therapies, given mechanistic interplay between the two proteinopathies [47].

3. Neuroinflammation and Microglial Modulation

3.1 Rationale

Genome-wide association studies (GWAS) have identified numerous risk variants in immune-related genes, including *TREM2*, *CD33*, and *CR1*, implicating microglial dysfunction in AD pathogenesis [48]. Pathological studies demonstrate activated microglia and elevated cytokine release in affected regions, suggesting that maladaptive immune responses contribute to synaptic loss and neurodegeneration [49].

3.2 TREM2 Agonism

TREM2, a receptor expressed on microglia, plays a critical role in phagocytosis and amyloid clearance. Agonistic antibodies such as AL002 are being evaluated in early-phase clinical trials. Initial reports indicate acceptable safety and pharmacodynamic effects, including increased soluble TREM2 levels in CSF and shifts in microglial activation states [50]. Clinical efficacy data, however, remain pending.

3.3 Colony-Stimulating Factor 1 Receptor (CSF1R) Inhibition

CSF1R inhibitors, developed to modulate microglial proliferation, have shown preclinical promise but carry risks of broad immunosuppression. Early human trials have demonstrated target engagement but raised concerns about off-target toxicities [51]. Whether these agents can be safely tailored for long-term AD treatment remains uncertain.

3.4 Anti-Inflammatory Small Molecules

Repurposing of nonsteroidal anti-inflammatory drugs (NSAIDs) and novel small molecules targeting inflammasome pathways has so far yielded inconclusive results in AD populations. More promising are brain-penetrant inhibitors of NLRP3 inflammasome signaling, which in preclinical models reduce amyloid burden and rescue synaptic function [52]. First-in-human studies are ongoing, though phase 3 efficacy data are not yet available.

3.5 Complement Pathway Modulation

The complement cascade, a key component of innate immunity, has been implicated in synaptic pruning in AD. Inhibitors of complement component C1q are in early-phase evaluation. Preliminary human safety data suggest tolerability, but efficacy signals remain to be established [53].

3.6 Summary of Neuroinflammation Trials

While amyloid and tau immunotherapies have advanced to late-phase and regulatory approvals, neuroinflammatory interventions remain **largely experimental**. Nonetheless, given the genetic and mechanistic evidence linking immune dysregulation to AD, these pathways represent highly promising targets for next-generation therapies [54].

4. Metabolic and Endocrine Approaches

4.1 Glucagon-Like Peptide-1 (GLP-1) Receptor Agonists

The incretin system has gained attention as a therapeutic target due to evidence linking impaired insulin signaling to AD pathophysiology. GLP-1 receptor agonists, widely used in type 2 diabetes, cross the blood–brain barrier and exert neuroprotective effects in preclinical models by reducing neuroinflammation, enhancing synaptic plasticity, and improving mitochondrial function [55].

Clinical translation has advanced rapidly. A phase 2 trial of liraglutide in AD demonstrated favorable safety and trends toward preserved cerebral glucose metabolism on FDG-PET, though without significant cognitive benefit over 12 months [56]. More recently, semaglutide, with higher potency and longer half-life, has entered phase 3 development (EVOKE and EVOKE+ trials). Preliminary reports indicate acceptable tolerability, with efficacy results expected in 2025 [57]. Given their established cardiovascular and metabolic benefits, GLP-1 agonists represent a particularly attractive class for patients with AD and comorbid metabolic disease.

4.2 Intranasal Insulin

Insulin resistance in the brain has been implicated in synaptic dysfunction and amyloid accumulation. Intranasal delivery bypasses the blood–brain barrier, achieving central nervous system penetration without systemic hypoglycemia [58]. Several small RCTs have shown that intranasal insulin improves working memory and functional connectivity on neuroimaging in patients with mild cognitive impairment (MCI) and early AD [59]. However, the phase 2 *SNIFF* trial reported no significant effect on primary cognitive endpoints, though exploratory subgroup analyses suggested possible benefit in APOE ε4 non-carriers [60].

Limitations include heterogeneity in dosing devices, formulations, and trial populations. Standardization of delivery methods will be essential before large-scale phase 3 trials can be conclusive.

4.3 Other Metabolic Pathways

Other metabolic modulators under exploration include peroxisome proliferator-activated receptor (PPAR) agonists, mitochondrial-targeted antioxidants, and ketone ester supplementation. While mechanistically plausible, most remain in early clinical stages with insufficient evidence to support efficacy [61].

5. Device-Enabled Interventions

5.1 Focused Ultrasound (FUS)

Non-invasive low-intensity focused ultrasound, often combined with intravenous microbubbles, transiently opens the blood–brain barrier (BBB), enhancing drug delivery and promoting amyloid clearance by activating microglia. Pilot human studies have shown feasibility and safety, with localized reductions in amyloid PET signal after repeated sessions [62]. However, clinical efficacy remains unproven, and larger trials are ongoing to assess whether BBB modulation can synergize with antibody therapies [63].

5.2 Photobiomodulation and Transcranial Stimulation

Photobiomodulation (near-infrared light therapy) and non-invasive brain stimulation techniques such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) have been studied as cognitive enhancers. Some small RCTs report improvements in executive function and memory, potentially through modulation of network connectivity [64]. Nevertheless, reproducibility has been limited, and effects are generally modest. These approaches are considered adjunctive rather than disease-modifying.

5.3 Intranasal Delivery Platforms

Beyond insulin, intranasal administration is being explored for a range of agents including antibodies, peptides, and nanoparticles. This route offers the advantage of bypassing systemic metabolism while targeting olfactory and trigeminal nerve pathways to the CNS. Early-phase trials are ongoing, though robust clinical outcomes are not yet available [65].

6. Biomarkers and Diagnostic Advances

6.1 Plasma Amyloid and Tau Markers

The past five years have seen a paradigm shift in AD diagnostics driven by blood-based biomarkers. Plasma phosphorylated tau species, particularly p-tau181, p-tau217, and p-tau231, have consistently shown high accuracy in differentiating AD from other dementias, with AUC values exceeding 0.90 in multiple cohorts [66]. These biomarkers not only predict amyloid and tau PET positivity but also correlate with longitudinal cognitive decline [67].

6.2 Neurofilament Light Chain (NfL) and Glial Fibrillary Acidic Protein (GFAP)

NfL reflects axonal damage, while GFAP reflects astroglial activation. Both can be measured reliably in plasma using ultrasensitive assays. Elevated GFAP levels have been shown to predict amyloid positivity even in preclinical stages, suggesting utility as an early screening tool [68]. NfL, while less specific, has strong prognostic value for disease progression across neurodegenerative conditions [69].

6.3 Integration into Clinical Trials

Blood biomarkers are rapidly being incorporated as inclusion criteria, pharmacodynamic readouts, and surrogate endpoints in therapeutic trials. For example, lecanemab and donanemab studies demonstrated significant reductions in plasma p-tau217 that paralleled amyloid clearance and clinical benefit [70]. This integration facilitates smaller, more efficient trials while reducing reliance on costly PET imaging and invasive lumbar puncture.

6.4 Digital Biomarkers and Wearables

Beyond molecular assays, digital biomarkers derived from wearable devices, smartphone applications, and passive monitoring systems are gaining traction. These technologies enable continuous assessment of mobility, sleep, and cognitive performance, providing real-world endpoints that may be more sensitive than traditional clinic-based assessments [71]. Integration of digital biomarkers into clinical trials remains in its infancy but is likely to expand in the near future.

7. Emerging and Adjunctive Strategies

7.1 Microbiome and Gut-Brain Axis

Evidence linking gut microbiota composition to AD pathology has prompted exploration of probiotics, prebiotics, and fecal microbiota transplantation. Early-phase trials demonstrate feasibility and potential effects on systemic inflammation, though cognitive outcomes are inconsistent [72].

7.2 Lifestyle-Based Multidomain Interventions

Multimodal lifestyle programs integrating diet, exercise, cognitive training, and vascular risk control, such as the FINGER trial framework, continue to demonstrate modest cognitive benefits in at-risk populations. Ongoing studies are testing whether these interventions can delay onset or enhance responsiveness to pharmacologic therapies [73].

Table 1. Overview of Emerging Therapeutic and Diagnostic Strategies in Alzheimer's Disease (2020–2025)

Therapeutic/Diagnostic Class	Representative Agents/Methods	Trial Phase	Key Findings	Limitations
Amyloid antibodies	Lecanemab, Donanemab	Phase 3	Slowing of decline (27–40%), amyloid clearance, p-tau reduction	ARIA risk, stage-dependent efficacy
Tau therapies	Semorinemab, Gosuranemab, AADvac1	Phase 2	Target engagement, limited clinical benefit	No phase 3 success, likely requires earlier use
Neuroinflammation	AL002 (TREM2 agonist), CSF1R inhibitors	Phase 1–2	Biomarker modulation, safe in early trials	Clinical efficacy unproven
Metabolic modulation	Liraglutide, Semaglutide, Intranasal insulin	Phase 2–3	Safe, possible cognitive/metabolic effects	Mixed results, device heterogeneity
Device-assisted	Focused ultrasound, Photobiomodulation	Pilot–Phase 2	Feasible, localized amyloid reduction	No definitive efficacy

Biomarkers	Plasma p-tau217, GFAP, NfL, digital endpoints	Validation studies	High diagnostic/prognostic accuracy	Need for standardization, assay variability
Adjunctive strategies	Microbiome modulation, Lifestyle interventions	Early phase	Biological plausibility, modest benefits	Heterogeneous outcomes, small studies

Discussion

The therapeutic landscape of Alzheimer's disease has undergone a profound transformation over the last five years. Where previously only symptomatic therapies were available, recent phase 3 successes with anti-amyloid antibodies have validated the concept of disease modification and reshaped both regulatory frameworks and clinical expectations. However, these advances represent only an initial step. The discussion below synthesizes the implications of recent trial findings, highlights persistent challenges, and explores emerging strategies that may define the next era of AD treatment.

1. Validating the Amyloid Hypothesis

The clinical efficacy demonstrated by lecanemab and donanemab has resolved decades of uncertainty surrounding the amyloid hypothesis. Both agents produced statistically significant, albeit modest, slowing of decline in early symptomatic AD [32,36]. Their parallel biomarker profiles—rapid amyloid clearance coupled with reductions in plasma p-tau—offer mechanistic evidence that targeting amyloid can attenuate downstream tau pathology. This convergence of clinical and biomarker outcomes provides the most compelling validation to date that amyloid is not merely an epiphenomenon but a driver of disease progression [33,37,42].

Nevertheless, these benefits must be contextualized. A 27–40% slowing of decline, though clinically meaningful, does not halt disease progression. Treatment must therefore be initiated **early**, prior to extensive neuronal loss. This imperative underscores the need for robust presymptomatic detection tools, such as blood-based biomarkers and digital monitoring, to enable timely therapeutic intervention [66–71]. Moreover, safety considerations remain a major limitation. Amyloid-related imaging abnormalities (ARIA) affect up to one-quarter of treated patients, particularly APOE ε4 homozygotes, complicating widespread implementation [34,38]. Future research should aim to optimize dosing, develop predictive biomarkers for ARIA, and explore adjunctive strategies to mitigate risk.

2. Tau as a Parallel and Complementary Target

If amyloid is an upstream initiator, tau pathology is more closely correlated with clinical symptoms and progression rate. Yet, to date, tau-targeted therapies have largely failed to demonstrate efficacy in symptomatic populations [43–46]. Several explanations are plausible. First, once widespread tangles are established, immunotherapy may be incapable of reversing damage. Second, trial populations have often included moderate-stage patients, when interventions are likely too late. Finally, heterogeneity in tau conformers and regional deposition may limit the efficacy of single-target antibodies.

Future approaches may require:

1. **Earlier intervention**, potentially in preclinical stages, enabled by plasma tau biomarkers [66–68].
2. **Combination therapies**, in which amyloid clearance reduces seeding while tau therapies address local propagation [47].
3. **Alternative modalities**, including vaccines, antisense oligonucleotides, or small molecules targeting tau phosphorylation and acetylation.

Although setbacks have tempered enthusiasm, tau remains an indispensable therapeutic target. The progression of tau pathology most directly predicts cognitive decline, and failure to address it will limit the overall effectiveness of amyloid-directed regimens.

3. The Central Role of Neuroinflammation

Neuroinflammatory mechanisms are increasingly recognized as a third pillar of AD pathophysiology, alongside amyloid and tau. GWAS findings implicating *TREM2* and *CD33* variants provide strong genetic validation for targeting microglial pathways [48]. Yet clinical translation is in its infancy. Early-phase trials of TREM2 agonists and CSF1R inhibitors demonstrate pharmacodynamic effects but no definitive clinical signals [50,51].

Several challenges complicate the development of anti-inflammatory strategies:

- Microglial activation can be both protective and detrimental, depending on context.
- Long-term immune modulation risks infection and systemic side effects.
- Patient stratification based on inflammatory biomarker profiles may be necessary to identify likely responders.

Despite these challenges, the rationale for immunomodulation remains compelling. Unlike amyloid and tau, which represent discrete pathologies, neuroinflammation intersects with multiple pathogenic processes, including synaptic pruning, oxidative stress, and vascular dysfunction [49,52,53]. Successful therapies may require nuanced modulation rather than broad suppression of immune activity.

4. Expanding Horizons: Metabolism, Devices, and the Gut-Brain Axis

Metabolic interventions offer an attractive avenue, particularly given the high prevalence of metabolic comorbidities in AD populations. GLP-1 receptor agonists such as semaglutide are especially promising, with dual systemic and neuroprotective benefits [55–57]. Should ongoing phase 3 trials confirm efficacy, these agents could become first-line adjuncts, bridging neurology and endocrinology.

Intranasal insulin illustrates both the potential and pitfalls of metabolic therapy. While mechanistically compelling, trial outcomes have been inconsistent, partly due to variability in delivery devices [59,60]. Standardization of administration technology will be critical for definitive evaluation.

Device-based interventions such as focused ultrasound represent another frontier. By transiently opening the blood–brain barrier, ultrasound may enable synergistic use with antibody therapies, enhancing brain penetration [62,63]. Photobiomodulation and transcranial stimulation, though less mechanistically grounded, may serve as supportive cognitive enhancers [64]. These approaches exemplify a growing emphasis on non-pharmacologic tools to complement traditional therapeutics.

The gut-brain axis has also emerged as a compelling area of investigation. While preliminary human trials remain small and heterogeneous, modulation of the microbiome may offer systemic benefits that extend to neurodegeneration [72]. As with lifestyle-based multidomain interventions, these strategies align with preventive paradigms, addressing risk factors years before symptom onset [73].

5. The Revolution in Biomarkers

Perhaps the most transformative development in recent years is the maturation of blood-based biomarkers. Plasma p-tau217 and p-tau231 now rival PET in diagnostic accuracy and enable efficient screening for therapeutic trials [66–70]. GFAP and NfL extend this toolkit, offering markers of astroglial activation and neurodegeneration [68,69].

The implications are profound:

- **Clinical trials** can be smaller, faster, and more representative.
- **Primary care** screening for AD risk is becoming feasible, supporting earlier intervention.
- **Therapeutic monitoring** can be conducted non-invasively, enabling dynamic adjustment of treatment regimens.

Digital biomarkers, while less mature, add a complementary layer of longitudinal functional assessment. Passive data from smartphones and wearables may capture subtle changes in cognition and behavior long before clinic-based tests detect decline [71]. The convergence of molecular and digital biomarkers points toward a future of personalized, precision AD medicine.

6. The Case for Combination Therapy

The cumulative evidence suggests that no single-target therapy will be sufficient to halt AD progression. The modest effects of amyloid antibodies highlight both the promise and the limitations of monotherapy. Analogies to oncology and HIV treatment suggest that **rational combinations**—targeting amyloid, tau, inflammation, and metabolism in parallel—may be necessary to achieve durable control.

Such strategies will require advances in trial design, regulatory flexibility, and biomarker-driven stratification. Adaptive platform trials, akin to those deployed in oncology, could accelerate evaluation of multi-drug regimens. Equally important will be the careful sequencing of therapies, as amyloid clearance may sensitize patients to subsequent tau-directed or inflammatory interventions [47].

7. Clinical and Ethical Considerations

While scientific progress is undeniable, clinical implementation poses practical and ethical challenges. Antibody therapies are costly, require repeated infusions, and necessitate MRI monitoring for ARIA. These demands risk exacerbating disparities in access, particularly in resource-limited settings [34,38]. Moreover, as presymptomatic treatment becomes possible, questions of overdiagnosis, psychological impact, and insurance implications will intensify.

Addressing these concerns will require integrated health policy, equitable reimbursement structures, and public education. The transition from symptomatic to disease-modifying therapy in AD represents not only a scientific shift but also a societal one.

8. Future Directions

Looking ahead, several priorities emerge:

1. **Earlier intervention**, ideally in preclinical populations identified through plasma biomarkers.
2. **Combination regimens**, modeled on other chronic progressive diseases.
3. **Personalized therapy**, guided by genetic, biomarker, and digital profiles.
4. **Global accessibility**, ensuring that breakthroughs do not widen existing disparities.

The next five years are likely to see expanded approvals of amyloid and metabolic therapies, maturation of tau and inflammation strategies, and integration of biomarkers into routine practice. Together, these advances suggest a trajectory toward a more comprehensive, precision-medicine approach to AD.

Summary of Discussion

In sum, the validation of amyloid-targeting therapies marks a watershed moment in AD therapeutics. Yet, their modest efficacy and safety limitations highlight the need for broader, multi-target approaches. Tau, neuroinflammation, metabolism, and the gut-brain axis represent key frontiers, while biomarkers have redefined both research and clinical practice. The future of AD treatment lies not in single interventions but in coordinated, combination-based, biomarker-driven strategies that address the disease's multifactorial biology.

Conclusions

Alzheimer's disease (AD) research has entered a new era, marked by the first generation of disease-modifying therapies and an expanding portfolio of mechanistic targets. Over the past five years, advances in amyloid-directed antibodies have provided the clearest validation yet that modifying core pathological processes can slow cognitive and functional decline. The approval of lecanemab and the strong evidence supporting donanemab represent milestones that have reshaped both therapeutic expectations and the global research agenda [32,36–38]. These therapies demonstrate that AD is modifiable, even if the degree of benefit remains modest and accompanied by important safety considerations such as amyloid-related imaging abnormalities.

The therapeutic pipeline now reflects a growing recognition that AD cannot be addressed through a single mechanistic pathway. While amyloid clearance offers measurable clinical gains, tau pathology, neuroinflammation, metabolic dysfunction, and vascular factors each contribute to disease progression in distinct yet interconnected ways. Therapies targeting tau, including monoclonal antibodies and antisense oligonucleotides, have so far yielded disappointing results in symptomatic populations, but remain promising for earlier intervention and as part of combination approaches [43–47]. Similarly, neuroinflammatory modulation is in its infancy but is supported by strong genetic and mechanistic evidence implicating microglial dysregulation [48–53]. The continued diversification of therapeutic modalities underscores the field's shift toward a systems-level view of AD biology.

Equally transformative has been the maturation of biomarkers. Plasma-based assays for phosphorylated tau isoforms, glial fibrillary acidic protein, and neurofilament light chain now rival established imaging modalities in diagnostic accuracy [66–70]. These tools enable earlier and less invasive diagnosis, reduce trial costs, and provide dynamic measures of treatment response. When combined with emerging digital biomarkers from wearable devices and smartphone-based monitoring, clinicians may soon be able to diagnose, monitor, and tailor treatment strategies in real time [71]. This biomarker revolution is essential to realizing the full potential of disease-modifying therapies, as timely identification of at-risk individuals will allow treatment initiation before irreversible neurodegeneration has occurred.

Despite these breakthroughs, significant challenges remain. The modest efficacy of current amyloid antibodies highlights the need for more potent or synergistic interventions. Safety concerns, particularly ARIA

in APOE ε4 carriers, limit applicability and necessitate ongoing surveillance [34,38]. Cost and infrastructure requirements raise ethical questions about equitable access, especially in low- and middle-income countries. Moreover, as treatment shifts earlier into the preclinical stage, concerns about overdiagnosis, patient autonomy, and psychosocial impact will demand careful policy and clinical guidance.

The future trajectory of AD therapy is likely to parallel the evolution of treatment in oncology and infectious diseases, where multi-target combination regimens ultimately transformed outcomes. Rationally designed therapeutic cocktails—integrating amyloid clearance, tau suppression, neuroinflammation modulation, and metabolic support—may offer synergistic benefits greater than the sum of their parts. Such strategies will require adaptive trial designs, regulatory innovation, and refined biomarker-based stratification to identify the right therapy for the right patient at the right time.

In addition to pharmacological approaches, lifestyle modification and preventive strategies will remain central. Multidomain interventions targeting diet, physical activity, vascular health, and cognitive engagement have demonstrated efficacy in reducing dementia risk at the population level [73]. Integrating these approaches with pharmacologic regimens offers a comprehensive, lifespan-based strategy to reduce incidence, delay onset, and slow progression.

Taken together, recent advances signal a turning point in AD therapeutics. After decades of frustration, the field now possesses the first disease-modifying agents, an expanding repertoire of mechanistic targets, and biomarker tools that make presymptomatic intervention a realistic goal. The next decade will determine whether these breakthroughs can be translated into durable clinical benefit on a population scale. Success will depend not only on scientific innovation but also on health system preparedness, equitable access, and societal engagement with the ethical challenges of early diagnosis and long-term treatment.

In conclusion, the treatment of Alzheimer's disease is transitioning from symptomatic management to precision, disease-modifying therapy. While current agents represent only an initial step, they have validated the principle that intervention can alter the course of the disease. The integration of amyloid, tau, inflammatory, metabolic, and lifestyle approaches—guided by advanced biomarkers—offers the most promising path toward meaningful disease control. Achieving this vision will require collaboration across disciplines, sustained investment, and a commitment to ensuring that advances benefit patients globally. Alzheimer's disease remains one of the greatest biomedical challenges of our time, but for the first time, the prospect of altering its trajectory is within reach.

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